(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 March 2004 (25.03.2004)

PCT

(10) International Publication Number
WO 2004/024710 A1

(51) International Patent Classification[7]: C07D 401/04, 403/04, 403/12, 401/14, 403/14, 417/14, A61K 31/4025, 31/428, 31/47, 31/517, 31/519, A61P 25/00

(21) International Application Number:
PCT/EP2003/010262

(22) International Filing Date:
11 September 2003 (11.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0221317.1 13 September 2002 (13.09.2002) GB
0305293.3 7 March 2003 (07.03.2003) GB

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

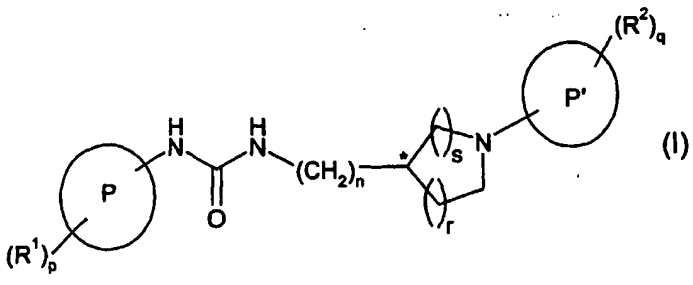
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/024710 A1

(54) Title: UREA COMPOUNDS ACTIVE AS VANILLOID RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PAIN



(57) Abstract: Certain compounds of formula (I): or a pharmaceutically acceptable salt or solvate thereof, wherein R^1, R^2, P, P', n, p, q, r and s are as defined in the specification, a process for preparing such compounds, a pharmaceutical composition comprising such compounds and the use of such compounds in medicine.

UREA COMPOUNDS ACTIVE AS VANILLOID RECEPTOR ANTAGONISTS FOR THE TREATMENT OF PAIN

This invention relates to novel compounds, especially urea derivatives, having pharmacological activity, processes for their preparation, to compositions containing them and to their use in medicine, especially in the treatment of various disorders.

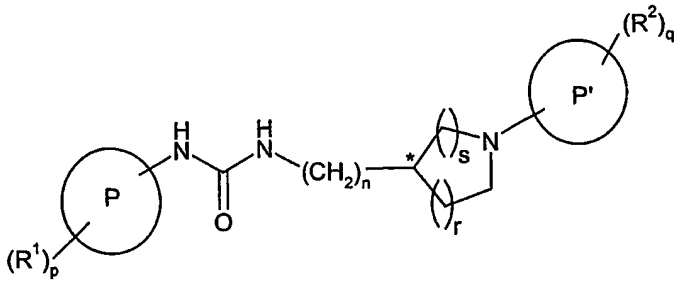
Vanilloids are a class of natural and synthetic compounds that are characterised by the presence of a vanillyl (4-hydroxy 3-methoxybenzyl) group or a functionally equivalent group. Vanilloid Receptor (VR-1), whose function is modulated by such compounds, has been widely studied and is extensively reviewed by Szallasi and Blumberg (The American Society for Pharmacology and Experimental Therapeutics, 1999, Vol. 51, No. 2.).

A wide variety of Vanilloid compounds of different structures are known in the art, for example those disclosed in European Patent Application Numbers, EP 0 347 000 and EP 0 401 903, UK Patent Application Number GB 2226313 and International Patent Application, Publication Numbers WO 92/09285, WO 02/100819, WO 02/076946, WO 02/090326 and WO 02/072536. Particularly notable examples of vanilloid compounds or vanilloid receptor modulators are capsaicin or trans 8-methyl-N-vanillyl-6-nonenamide which is isolated from the pepper plant, capsazepine (*Tetrahedron*, **53**, 1997, 4791) and olvanil or - N-(4-hydroxy-3-methoxybenzyl)oleamide (*J. Med. Chem.*, **36**, 1993, 2595).

US Patent Numbers, US 3,424,760 and US 3,424,761 both describe a series of 3-Ureidopyrrolidines that are said to exhibit analgesic, central nervous system, and pyschopharmacological activities. These patents specifically disclose the compounds 1-(1-phenyl-3-pyrrolidinyl)-3-phenyl urea and 1-(1-phenyl-3-pyrrolidinyl)-3-(4-methoxyphenyl)urea respectively.

International Patent Applications, Publication Numbers WO 02/08221, WO 02/16317, WO 02/16318, WO 02/16319, WO 03/022809 and WO 03/052945 each disclose certain vanilloid receptor antagonists and their use in the treatment of diseases associated with the activity of the vanilloid receptor.

According to a first aspect of the present invention, there is provided a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:

P is selected from benzisothiazolyl, cinnolinyl, phenyl, phthalazinyl, quinazolinyl, quinolinyl or iso-quinolinyl;

P' is selected from cinnolinyl, phenyl, pyridazinyl, pyridinyl, pyrimidinyl, thiazolyl, quinolinyl or iso-quinolinyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, $-NO_2$, -OH, $-OCF_3$, $-CF_3$, $-NR^4R^5$, $-S(O)_mR^6$, $-S(O)_2NR^4R^5$, $-OS(O)_2R^6$, $-OS(O)_2CF_3$, $-O(CH_2)_xNR^4R^5$, $-C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, $-C(O)(CH_2)_xOR^6$, $-C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, $-C(O)NR^4R^5$, $-(CH_2)_xC(O)$alkoxy, $-(CH_2)_xOC(O)R^6$, $-(CH_2)_xOR^6$, $-(CH_2)_xR^4R^5$, $-(CH_2)_xC(O)NR^4R^5$, $-(CH_2)_xN(R^4)C(O)R^6$, $-(CH_2)_xS(O)_2NR^4R^5$, $-(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, $-(CH_2)_xS(O)_2R^6$, $-(OCH_2)_xS(O)_2R^6$, $-N(R^4)S(O)_2R^6$, $-N(R^4)C(O)R^6$, $-(CH_2)_xN(R^4)S(O)_2R^6$, $-(CH_2)_xN(R^4)C(O)R^6$ or $-(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

Z is a bond, O, S or NR^7;

R^6 is alkyl or aryl;

R^7 is hydrogen, alkyl or aryl;

Ar is phenyl, which may be optionally substituted by one or more halo atoms;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

with the proviso that when P is phenyl, quinolinyl or iso-quinolinyl then P' is cinnolinyl, pyridazinyl, pyrimidinyl, thiazolyl, quinolinyl or iso-quinolinyl.

Suitably, P is phenyl, 7-benzisothiazolyl, 5-cinnolinyl, 5-phthalazinyl, 8-quinazolinyl, 5-quinolinyl, 7-quinolinyl, 5-isoquinolinyl or 8-isoquinolinyl. Preferably, P is phenyl. More preferably, P is cinnolinyl or benzisothiazolyl. Most preferably, P is cinnolinyl.

Suitably, P' is phenyl, 2-pyridinyl, 2-pyrimidinyl, 3-pyridazinyl, 2-thiazolyl, 5-cinnolinyl, 5-quinolinyl or 5-isoquinolinyl. Preferably, P' is pyridinyl or iso-quinolinyl. Most preferably, P' is pyridinyl.

Suitably, R^1 is halo, alkyl, alkoxy, -CN, $-CF_3$ or $-OCF_3$. Preferably, R^1 is fluoro, chloro, bromo, methyl, *tert*-butyl, *iso*-propoxy, -CN, $-CF_3$ or $-OCF_3$.

When p is 2 or 3 the groups R^1 may be the same or different.

Suitably, p is 1 or 2.

Suitably, n is 0 or 1. Preferably, n is 0.

Suitably, R^2 is halo, alkyl, alkoxy, -CN or CF_3. Preferably, R^2 is chloro, bromo, methyl, methoxy, -CN or $-CF_3$.

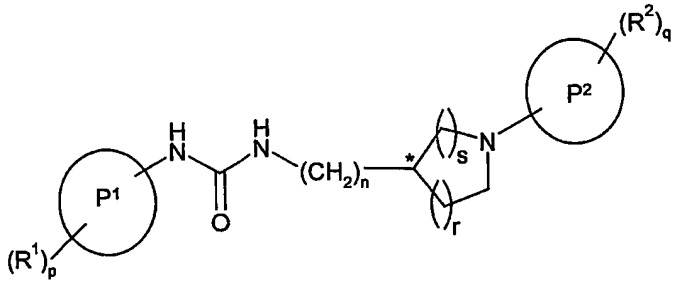
When q is 2 or 3 the groups R^2 may be the same or different.

Suitably, q is 1 or 2.

Suitably, r and s have values such that they define a 4 - 7 membered ring. Preferably, r and s have values such that they define a 5 or 6 membered ring, most preferably a 5 membered ring.

Suitably, x is 1, 2 or 3.

According to a further aspect of the present invention, there is provided a subset of compounds of formula (I), of formula (IA),



(IA)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:

P^1 is selected from benzisothiazolyl, cinnolinyl, phthalazinyl or quinazolinyl;

P^2 is selected from cinnolinyl, pyridazinyl, pyrimidinyl, thiazolyl, quinolinyl or isoquinolinyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, $-NO_2$, -OH, $-OCF_3$, $-CF_3$, $-NR^4R^5$, $-S(O)_mR^6$, $-S(O)_2NR^4R^5$, $-OS(O)_2R^6$, $-OS(O)_2CF_3$, $-O(CH_2)_xNR^4R^5$, $-C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, $-C(O)(CH_2)_xOR^6$, $-C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, $-C(O)NR^4R^5$, $-(CH_2)_xC(O)$alkoxy, $-(CH_2)_xOC(O)R^6$, $-(CH_2)_xOR^6$, $-(CH_2)_xR^4R^5$, $-(CH_2)_xC(O)NR^4R^5$, $-(CH_2)_xN(R^4)C(O)R^6$, $-(CH_2)_xS(O)_2NR^4R^5$, $-(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, $-(CH_2)_xS(O)_2R^6$, $-(OCH_2)_xS(O)_2R^6$, $-N(R^4)S(O)_2R^6$, $-N(R^4)C(O)R^6$, $-(CH_2)_xN(R^4)S(O)_2R^6$, $-(CH_2)_xN(R^4)C(O)R^6$ or $-(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

Z is a bond, O, S or NR^7;

R^6 is alkyl or aryl;

R^7 is hydrogen, alkyl or aryl;

Ar is phenyl, which may be optionally substituted by one or more halo atoms;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6.

Suitably, P^1 is cinnolinyl or benzisothiazolyl. Preferably, P^1 is cinnolinyl.

Suitably, P^2 is pyridazinyl, pyrimidinyl or iso-quinolinyl. Preferably, P^2 is iso-quinolinyl.

Suitably, R^1 is halo, alkyl, alkoxy, -CN, $-CF_3$ or $-OCF_3$. Preferably, R^1 is alkyl. Most preferably, R^1 is methyl.

When p is 2 or 3 the groups R^1 may be the same or different.

Suitably, p is 1 or 2.

Suitably, n is 0 or 1. Preferably, n is 0.

Suitably, R^2 is halo, alkyl, alkoxy, -CN or $-CF_3$. Preferably, R^2 is methyl or $-CF_3$.

When q is 2 or 3 the groups R^2 may be the same or different.

Suitably, q is 1 or 2.

Suitably, r and s have values such that they define a 4 - 7 membered ring. Preferably, r and s have values such that they define a 5 or 6 membered ring, most preferably a 5 membered ring.

Suitably, x is 1, 2 or 3.

Compounds of formula (I) of particular interest according to the present invention are Examples 1 - 74 or pharmaceutically acceptable salts or solvates thereof.

Certain of the carbon atoms of formula (I) are chiral carbon atoms, such as the carbon atom marked with an "*", and therefore compounds of formula (I) may exist as stereoisomers. The invention extends to all optical isomers such as stereoisomeric forms of the compounds of formula (I) including enantiomers and mixtures thereof, such as racemates. The different stereoisomeric forms may be separated or resolved one from the other by conventional methods or any given isomer may be obtained by conventional stereospecific or asymmetric syntheses.

Preferred compounds of formula (I) have the C* carbon in the R-configuration.

Certain of the compounds herein can exist in various tautomeric forms and it is to be understood that the invention encompasses all such tautomeric forms.

As indicated above, the compounds of formula (I) can form salts, especially pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts are those use conventionally in the art and include those described in *J. Pharm. Sci.*, 1977, **66**, 1-19, such as acid addition salts.

Suitable pharmaceutically acceptable salts include acid addition salts.

Suitable pharmaceutically acceptable acid addition salts include salts with inorganic acids such, for example, as hydrochloric acid, hydrobromic acid, orthophosphoric acid or sulphuric acid, or with organic acids such, for example as methanesulphonic acid, toluenesulphonic acid, acetic acid, propionic acid, lactic acid, citric acid, fumaric acid, malic acid, succinic acid, salicylic acid, maleic acid, glycerophosphoric acid or acetylsalicylic acid.

The salts and/or solvates of the compounds of the formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the preparation of pharmaceutically acceptable salts and/or solvates of compounds of formula (I) or the compounds of the formula (I) themselves, and as such form another aspect of the present invention.

The compounds of formula (I) may be prepared in crystalline or non-crystalline form, and if crystalline, may be optionally hydrated or solvated. This invention includes in its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

Suitable solvates include pharmaceutically acceptable solvates, such as hydrates.

Solvates include stoichiometric solvates and non-stoichiometric solvates.

As used herein the term "alkyl" as a group or part of a group refers to a straight or branched chain saturated aliphatic hydrocarbon radical containing 1 to 12 carbon atoms, suitably 1 to 6 carbon atoms. Such alkyl groups in particular include methyl ("Me"), ethyl ("Et"), n-propyl ("Pr^n"), *iso*-propyl ("Pr^i"), n-butyl ("Bu^n"), *sec*-butyl ("Bu^s"), *tert*-butyl ("Bu^t"), pentyl and hexyl. Where appropriate, such alkyl groups may be substituted by one or more groups selected from halo

(such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{2-6} alkenyl, C_{3-6} alkynyl, C_{1-6} alkoxy, aryl and di-C_{1-6} alkylamino.

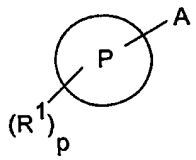
As used herein, the term "alkoxy" as a group or part of a group refers to an alkyl ether radical, wherein the term "alkyl" is defined above. Such alkoxy groups in particular include methoxy, ethoxy, n-propoxy, *iso*-propoxy, n-butoxy, *iso*-butoxy, *sec*-butoxy and *tert*-butoxy. Where appropriate, such alkoxy groups may be substituted by one or more groups selected from halo (such as fluoro, chloro, bromo), -CN, -CF_3, -OH, –OCF_3, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-6} alkynyl, aryl and di-C_{1-6} alkylamino.

As used herein, the term "aryl" as a group or part of a group refers to a carbocyclic aromatic radical ("Ar"). Suitably such aryl groups are 5-6 membered monocyclic groups or 8-10 membered fused bicyclic groups, especially phenyl ("Ph"), biphenyl and naphthyl, particularly phenyl.

The term "halo" is used herein to describe, unless otherwise stated, a group selected from fluorine ("fluoro"), chlorine ("chloro"), bromine ("bromo") or iodine ("iodo").

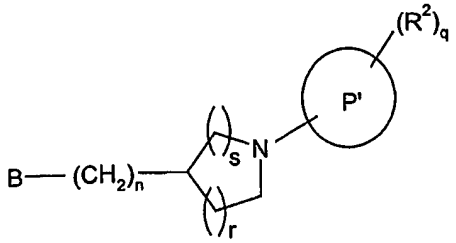
The term "naphthyl" is used herein to denote, unless otherwise stated, both naphth-1-yl and naphth-2-yl groups.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, which process comprises coupling a compound of formula (II):



(II)

in which R^1, P and p are as defined in formula (I) with a compound of formula (III):



(III)

in which P', R^2, n, q, r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety;

and thereafter, as necessary, carrying out one or more of the following reactions:

(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

Suitable examples of appropriate A and B groups include:

(a) A is -N=C=O and B is NH_2; or A is NH_2 and B is N=C=O or

(b) A is NH_2 and B is NH_2 together with an appropriate urea forming agent.

In process (a) the reaction is carried out in an inert solvent such as dichloromethane or acetonitrile.

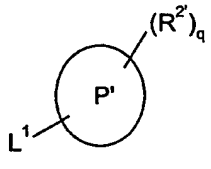
In process (b) the urea forming agent can be carbonyl diimidazole or phosgene or triphosgene, and carried out in an inert organic solvent such as diethyl ether, tetrahydrofuran or dichloromethane at ambient or elevated temperature in the presence of a base such as triethylamine or pyridine.

An alternative method of synthesis of the unsymmetrical urea compounds of formula (I) is from a diaryl carbonate, via the corresponding carbamate. Such a methodology is described by Freer et al. (Synthetic Communications, 26(2), 331 - 349, 1996). It would be appreciated by those skilled in the art that such a methodology could be readily adapted for preparation of the compounds of formula (I).

A further method of synthesis is using phenyl chloroformate as described by B.R.Baker *et al.*, J.Med.Chem., 1969, 12, 672-6.

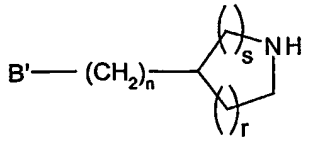
It will be appreciated by those skilled in the art that it may be necessary to protect certain reactive substituents during some of the above-mentioned procedures. Standard protection and deprotection techniques, such as those described in Greene T.W. 'Protective groups in organic synthesis', New York, Wiley (1981), can be used. For example, primary amines can be protected as phthalimide, benzyl, benzyloxycarbonyl or trityl derivatives. Carboxylic acid groups can be protected as esters. Aldehyde or ketone groups can be protected as acetals, ketals, thioacetals or thioketals. Deprotection of such groups is achieved using conventional procedures well known in the art.

A compound of formula (III) may be prepared by reaction of a compound of formula (IV):



(IV)

wherein, P' is as defined in relation to formula (I) and $R^{2'}$ is R^2 as defined above or a protected form thereof, L^1 is a leaving group and q is as defined above, with a compound of formula (V):



(V)

wherein B' is B as defined above or a protected form thereof and n, r and s are as defined above.

Suitably L^1 is a halogen, such as chlorine.

Suitably, the compound of formula (V) is in an activated form, for example an ionic form. Such activated forms are prepared using conventional coupling reaction methodology, as for example by reacting compounds (IV) and (V) in the presence of an alkali carbonate, such as potassium carbonate, in an

aprotic solvent such as dimethylformamide using reaction conditions appropriate to the particular methodology chosen, for example at an elevated temperature, such as 100°C.

Compounds of formulae (IV) and (V) are commercially available, or are prepared by known procedures, such as those disclosed in: *Heterocycles*, 1984, **22(1)**, 117 and J. Chem. Soc., Perkin 1, 1988, **4**, 921 for compounds of formula (IV) and *J. Med. Chem.*, 1992, **35(10)**, 1764 for compounds of formula (V), or by methods analogous to these disclosed methods.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative.

Compounds of formula (I) and their pharmaceutically acceptable salts or solvates thereof have Vanilloid receptor antagonist (VR1) activity and are believed to be of potential use for the treatment or prophylaxis of certain disorders, or treatment of the pain associated with them, such as: pain, chronic pain, neuropathic pain, postoperative pain, postrheumatoid arthritic pain, osteoarthritic pain, back pain, visceral pain, cancer pain, algesia, neuralgia, dental pain, headache, migraine, neuropathies, carpal tunnel syndrome, diabetic neuropathy, HIV-related neuropathy, post-herpetic neuralgia, fibromyalgia, neuritis, sciatica, nerve injury, ischaemia, neurodegeneration, stroke, post stroke pain, multiple sclerosis, respiratory diseases, asthma, cough, COPD, broncho constriction, inflammatory disorders, oesophagitis, heart burn, Barrett's metaplasia, dysphagia, gastroeosophageal relux disorder (GERD), stomach and duodenal ulcers, functional dyspepsia, irritable bowel syndrome, inflammatory bowel disease, colitis, Crohn's disease, pelvic hypersensitivity, pelvic pain, menstrual pain, renal colic, urinary incontinence, cystitis, burns, itch, psoriasis, pruritis, emesis (hereinafter referred to as the "Primary Disorders of the Invention").

The compounds of the present invention are also indicated to be useful in the treatment and/or prophylaxis of pelvic pain, renal colic, biliary colic, functional dyspepsia, Barrett's metaplasia, dysphagia and pain associated therewith (hereinafter referred to as the "Secondary Disorders of the Invention").

Accordingly, the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, for use as an active

therapeutic substance, in particular, in the treatment and/or prophylaxis of the Primary Disorders and/or Secondary Disorders of the Invention.

In particular, the invention provides a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof for use in the treatment or prophylaxis of pain.

The invention further provides a method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Primary Disorders of the Invention, in mammals including humans, which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention further provides a method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in particular the Secondary Disorders of the Invention, in mammals including humans, which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof.

The invention provides for the use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, particularly the Primary and/or Secondary Disorders of the Invention.

In order to use the compounds of the invention in therapy, they will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. Thus, the present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof and a pharmaceutically acceptable carrier or excipient therefor.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral, rectal administration or intravesical administration to the bladder and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable

powders, injectable or infusable solutions, suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the

weight of the sufferer, and other similar factors. For systemic administration, dosage levels from 0.01mg to 100mg per kilogramme of body weight are useful in the treatment of pain. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 20, 20 to 250, or 0.1 to 500.0 mg, for example 0.2 to 5 and 0.1 to 250 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.5 to 1000 mg; and such therapy may extend for a number of weeks or months.

No unacceptable toxicological effects are indicated with compounds of the invention when administered in accordance with the invention.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following Descriptions and Examples illustrate the preparation of the compounds of the invention.

Abbreviations

$MgSO_4$ - Magnesium sulfate
TFA – Trifluoroacetic acid
DCM - dichloromethane

Description 1

[(*R*)-1-(5-Trifluoromethylpyridin-2-yl)pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D1)

To a solution of 2-chloro-5-trifluoromethylpyridine (7.3g, 0.04mol) and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine (7.5g, 0.04mol) in dry dimethylformamide (100ml) was added powdered potassium carbonate (6.6g, 0.05mol) and the reaction heated at 100°C for 7h and cooled. Solvent was removed under reduced pressure and the residue partitioned between ethyl acetate and water. The organic phase was separated, dried ($MgSO_4$) and

filtered. Removal of solvent under reduced pressure gave a solid. Chromatography on silica gel eluting with ethyl acetate and DCM (gradient elution, 20% maximum) afforded the title compound as a white solid.

Description 2

(*R*)-1-(5-Trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine(D2)

A solution of D1 (11.5g, 0.04mol) in DCM (80ml) was cooled (ice-bath) and TFA (excess, 50ml) was added. Reaction was warmed to ambient temperature, stirred for 3h and partitioned between ethyl acetate and aqueous sodium hydroxide. The organic phase was separated, dried ($MgSO_4$) and filtered. Removal of solvent under reduced pressure afforded the crude product as a yellow oil. Bulb to bulb distillation under reduced pressure initially afforded the product as a oil which crystallised on standing.

Description 3

1,3-Dimethyl-5-nitroisoquinoline (D3)

1,3-Dimethylisoquinoline [(*Chem. Lett.*, 1983, p.791), 2.39g, 15.20mM], in conc. sulfuric acid, (15ml), was cooled to below 4°C. A solution of potassium nitrate, (1.69g, 16.72mM), in conc. sulfuric acid was added dropwise, maintaining the temperature below 4°C. After complete addition the solution was stirred at this temperature for a further 2h, then warmed to room temperature for 1h. The reaction mixture was poured into ice water and the solution basified with sodium hydroxide and extracted with DCM. The extract was washed with brine, dried and concentrated to a yellow solid. Purification by silica gel chromatography afforded the title compound as a yellow crystalline solid.

Description 4

5-Amino-1,3-dimethylisoquinoline (D4)

A solution of D3 (2.01g, 9.94mM) and 10% palladium on charcoal (1g) in methanol was hydrogenated at atmospheric pressure for 1h. The catalyst was filtered off and the filtrate concentrated under reduced pressure to afford the product as a cream coloured solid.

Description 5

3-Methyl-5-nitroisoquinoline (D5)

A solution of 3-methylisoquinoline (5.4g, 0.038mol) in conc. sulfuric acid (30ml) was cautiously added to a solution of potassium nitrate (4.25g, 1.1eq) in conc. sulfuric acid (23ml) whilst maintaining the temperature below 4°C (ice bath). Stirring was continued for 2h and then temperature raised to ambient. Reaction was further stirred for 3h and then poured into an ice-water slurry (500ml). Neutralisation using solid potassium carbonate afforded a yellow solid which was filtered and washed with water. This material was dissolved in ethanol (200ml), filtered and concentrated under reduced pressure to afford the title compound.

Description 6

5-Amino-3-methylisoquinoline (D6)

The title compound was prepared from D5 using the procedure outlined for Description 4.

Description 7

(1-Benzyl-piperidin-4-yl)-carbamic acid *tert*-butyl ester (D7)

To a solution of 1-benzyl-4-aminopiperidine (30g, 0.16mol) in DCM (200ml) was added dropwise a solution of di-*tert*-butyl dicarbonate (1.1eq.,

37.9g) in DCM (100ml) over a period of 2h. Reaction was stirred at ambient temperature for 18h and then solvent was removed under reduced pressure to afford the product as a white solid.

Description 8

Piperidin-4-yl-carbamic acid *tert*-butyl ester (D8)

A solution of D7 (10g, 3.4mmol) in methanol (150ml) was hydrogenated at 50psi in a Parr hydrogenator using 10% Palladium on carbon catalyst (800mg) for 18h. Catalyst was filtered off and the filtrate concentrated under reduced pressure to afford the product as a white solid.

Description 9

1-(5-Trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D9)

The title compound was prepared from D8 and 2-chloro-5-trifluoromethylpyridine using the procedure outlined for Descriptions D1 and D2.

Description 10

(*R*)-1-(3-Trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine(D10)

The title compound was prepared from 2-chloro-3-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 11

(*R*)-1-(4-Trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine(D11)

The title compound was prepared from 2-chloro-4-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 12

(*R*)-1-(6-Trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine(D12)

The title compound was prepared from 2-chloro-6-trifluoromethylpyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 13

(*R*)-1-(3-Chloropyridin-2-yl)pyrrolidin-3-ylamine(D13)

The title compound was prepared from 2,3-dichloropyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 14

(*R*)-1-(5-Chloropyridin-2-yl)pyrrolidin-3-ylamine(D14)

The title compound was prepared from 2,5-dichloropyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 15

(*R*)-1-(5-Bromopyridin-2-yl)pyrrolidin-3-ylamine(D15)

The title compound was prepared from 2-Chloro-5-bromopyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 16

(*R*)-1-(6-Methylpyridin-2-yl)pyrrolidin-3-ylamine(D16)

The title compound was prepared from 2-chloro-6-methylpyridine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 17

1-(3-Trifluoromethylpyridin-2-yl)piperidine-4-ylamine (D17)

The title compound was prepared from D8 and 2-chloro-3-trifluoromethylpyridine using the procedure outlined for Descriptions D1 and D2.

Description 18

1-(6-Trifluoromethylpyridin-2-yl)piperidin-4-ylamine(D18)

The title compound was prepared from D8 and 2-chloro-6-trifluoromethylpyridine using the procedure outlined for Descriptions D1 and D2.

Description 19

1-(4-Trifluoromethylpyridin-2-yl)piperidin-4-ylamine(D19)

The title compound was prepared from D8 and 2-chloro-4-trifluoromethylpyridine using the procedure outlined for Descriptions D1 and D2.

Description 20

1-(3-Chloro-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D20)

The title compound was prepared from D8 and 2,3-dichloro-5-trifluoromethylpyridine using the procedure outlined for Descriptions D1 and D2.

Description 21

((*R*)-1-Isoquinolin-5-ylpyrrolidin-3-yl)carbamic acid *t*-butyl ester (D21)

The title compound was prepared from (3*R*)-(+)-3-(*tert*-butoxycarbonylamino)pyrrolidine and 5-bromoisoquinoline, (Synthesis, 1975, p.733), using the procedure outlined for Description 1.

Description 22

(R)-1-Isoquinolin-5-ylpyrrolidin-3-ylamine (D22)

The title compound was prepared from D21 using the procedure outlined for Description D2.

Description 23

[(*R*)-1-(4-Trifluoromethylpyrimidin-2-yl)pyrrolidin-3-yl]-carbamic acid *tert*-butyl ester (D23)

The title compound was prepared from 2-chloro-4-trifluoromethylpyrimidine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Descriptions D1 and D2.

Description 24

(*R*)-1-(6-Trifluoromethylpyridazin-3-yl)pyrrolidin-3-ylamine (D24)

The title compound was prepared from 3-chloro-6-trifluoromethylpyridazine and 3*R*-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine using the procedure outlined for Description D1 and D2.

Description 25

1-(4-Trifluoromethylpyrimidin-2-yl)piperidin-4-ylamine (D25)

The title compound was prepared from D8 and 2-chloro-4-trifluoromethylpyrimidine using the procedure outlined for Descriptions D1 and D2.

The following amines were prepared using methods similar to those described above.

(*R*)-1-(3-Methylpyridin-2-yl)pyrrolidin-3-ylamine (D26).

(*R*)-1-(4-Methylpyridin-2-yl)pyrrolidin-3-ylamine (D27).

(*R*)-1-(5-Methylpyridin-2-yl)pyrrolidin-3-ylamine (D28).

(*R*)-1-(6-Methoxypyridin-2-yl)pyrrolidin-3-ylamine (D29).

1-(3-Cyano-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D30).

Description 31

8-Aminoquinazoline (D31)

4-Chloro-8-nitro-quinazoline (J. Org. Chem, 1947, 47, 405-421) (100mg) was dissolved in methanol (10ml), Pd on $CaCO_3$ (30mg) added and then hydrogenation at 50 psi for 16h. Catalyst was filtered through cellite and the filtrate concentrated under reduced pressure. The resulting solid was partitioned between sat $NaHCO_3$, and 20% methanol in DCM. Separation of the organic phase, drying over magnesium sulfate and removal of solvent under reduced pressure gave a solid. A solution of the solid in xylene (5ml) containing 10% Pd on C (5mg) was refluxed for 48h, cooled and filtered through Celite. Removal of solvent under reduced pressure afforded the product as a yellow solid.

(3*R*)-(+)-3-(*tert*-butyloxycarbonylamino)pyrrolidine, 5-aminoisoquinoline, 1-aminoisoquinoline, 5-aminoquinoline, 3-Methyl-5-aminocinnoline and 7-aminoquinoline are commercially available.

5-Aminophthalazine was prepared according to the procedure outlined in the literature (J. Chem Soc., Perkin Trans. 1, 1993, 2, 211-216).

8-Aminoquinazoline was prepared according to the procedure outlined in the literature (J. Org. Chem., 1947, 12, 405-421).

The following amines were prepared using methods similar to those described above.

(*R*)-1-(6-Methyl-5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D32).

(*R*)-1-(6-Methyl-4-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D33).

(*R*)-1-(6-Methyl-3-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D34).

(*R*)-1-(3-Chloro-5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D35).

(*R*)-1-(3-Bromo-5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D36).

1-(3-Chloropyridin-2-yl)piperidin-4-ylamine (D37).

1-(6-Methoxypyridin-2-yl)piperidin-4-ylamine (D38).

1-(6-Methyl-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D39).

1-(6-Methyl-4-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D40).

1-(3-Methyl-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D41).

1-(3-Bromo-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D42).

1-(6-Methoxy-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D43).

1-(3-Chloro-6-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D44).

1-(5-Chloro-6-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D45).

1-(3-Chloro-6-methoxypyridin-2-yl)piperidin-4-ylamine (D46).

1-(6-Methoxy-3-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D47).

1-(3-[4-Fluorophenyl]-5-trifluoromethylpyridin-2-yl)piperidin-4-ylamine (D48).

(*R*)-1-(3-Fluorophenyl)pyrrolidin-3-ylamine (D49).
Prepared as described in WO 02/090326.

(*R*)-1-(3,4-Difluorophenyl)pyrrolidin-3-ylamine (D50).
Prepared as described in WO 02/090326.

(*R*)-1-(3-Fluoro-4-methylphenyl)pyrrolidin-3-ylamine (D51).
Prepared as described in WO 02/090326.

(*R*)-1-(4-Trifluoromethylpyridin-2-yl)pyrrolidin-2-yl)methylamine (D52).
Prepared from (*R*)-2-*tert* butyldimethylsilyloxymethyl)pyrrolidine as described in WO 02/090326 and 2-chloro-4-trifluoromethylpyridine using the method of D1 and D2.

(*R*)-1-(5-Trifluoromethylpyridin-2-yl)pyrrolidin-2-yl)methylamine (D53).
Prepared from (*R*)-2-*tert* butyldimethylsilyloxymethyl)pyrrolidine as described in WO 02/090326 and 2-chloro-5-trifluoromethylpyridine using the method of D1 and D2.

(*R*)-1-(6-Trifluoromethylpyridin-2-yl)pyrrolidin-2-yl)methylamine (D54).
Prepared from (*R*)-2-*tert* butyldimethylsilyloxymethyl)pyrrolidine as described in WO 02/090326 and 2-chloro-6-trifluoromethylpyridine using the method of D1 and D2.

(*S*)-1-(5-Trifluoromethylpyridin-2-yl)pyrrolidin-2-yl)methylamine (D55).
Prepared from (*S*)-2-*tert* butyldimethylsilyloxymethyl)pyrrolidine as described in WO 02/090326 and 2-chloro-5-trifluoromethylpyridine using the method of D1 and D2.

1-(5-Chloro-6-methoxypyridin-2-yl)piperidin-4-ylamine (D56).

1-(4-Trifluoromethylthiazol-2-yl)piperidin-4-ylamine (D57).
Prepared from D8 and 2-bromo-4-trifluoromethylthiazole (J.A.Edwards Ger.Offen., 2252070, 1973) in a manner similar to that described in D1 and D2.

(*R*)-1-(5-Chloro-6-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D58).

(*R*)-1-(3-Methyl-5-trifluoromethylpyridin-2-yl)pyrrolidin-3-ylamine (D59).

7-Amino-3-methylbenzisothiazole (D60).
The title compound was prepared using a method similar to that described by K.Clarke *et al.*, J.Chem.Res, Synopses 1980, ***6***, 197.

Example 1

1-(4-*t*-Butylphenyl)-3-((R)-1-isoquinolin-5-ylpyrrolidin-3-yl)urea, hydrochloride salt (E1)

A solution of 4-*t*-butylphenylisocyanate (0.082g) in DCM (1ml) was added to (R)-1-Isoquinolin-5-ylpyrrolidin-3-ylamine (0.1g) in dry DCM (2ml). After 48h at 25^{0}C, the solution was chromatographed on silica gel with 5% methanol/ethyl acetate. Appropriate fractions gave a colourless solid. Methanol (3ml) was added followed by 1M HCl in ether (2ml) giving a yellow homogeneous solution. This was concentrated, triturated with ether and gave the *title compound* as a yellow solid, ^{1}H NMR (d_6-DMSO, 400MHz) δ 1.23 (9H, s), 1.96 (1H, m), 2.29 (1H, m), 3.39 (1H, m), 3.55 (1H, m), 3.73 (1H, m), 3.83 (1H, m), 7.21 (2H, d, J8.8Hz), 7.28 (2H, d, J8.8Hz), 7.42 (1H, d, J7.7Hz), 7.85 (1H, t, J8.0Hz), 7.92 (1H, d, J8.0Hz), 8.50 (1H, d, J6.8Hz), 8.64 (1H, m) and 9.79 (1H, s).

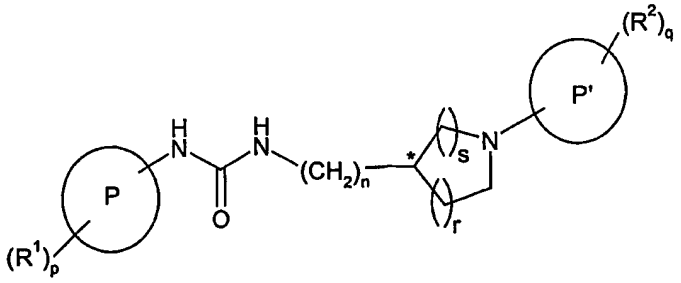
Example 2

1-Quinazolin-8-yl-3-[1-(5-trifluoromethylpyridin-2-yl)pyrrolidin-3-yl]-urea (E2)

D2 (56mg, 0.24mmol) in DCM (1ml) was added to a solution of the tricarbonate (64mg) in DCM (1ml). The mixture was stirred for 20min and resin bound trisamine (64mg) added. Stirred for 16h and filtered. D31 (35mg, 0.24mmol) was added as a solution in DCM (2ml), and the mixture stirred for 24h. The solvent was removed and the residue purified by flash chromatography (ethyl acetate:hexane eluent) to give the title compound as an off-white solid.
^{1}H NMR ($CDCl_3$, 400MHz) : δ 2.10-2.18(1H ,m), 2.33-2.41(1H, m), 3.53-3.69(3H, m), 3.80-3.85(1H, m), 4.64-4.70(1H, m), 5.88-5.89(1H, d), 6.31-6.33(1H, d), 7.45-7.46(1H, dd), 7.55-7.65(2H, m), 8.35-8.36(1H, d), 8.72-8.74(1H, dd), 8.80(1H, s), 9.08(1H, s), 9.31(1H, s).
MS: 402.38 ($C_{19}H_{17}F_3N_6O$); found: 401.3 (MS-, 100%)

The following Examples detailed in Table 1 (n = 0) below were prepared using similar methods to those described above.

Table 1



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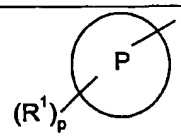
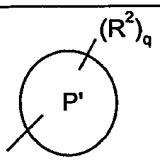
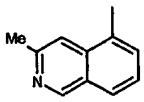
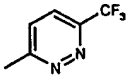
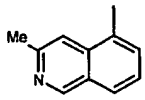
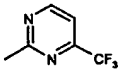
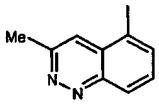
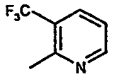
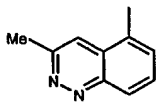
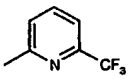
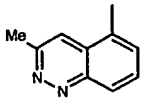
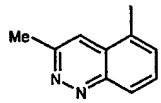
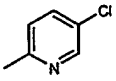
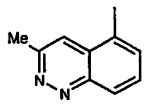
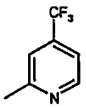
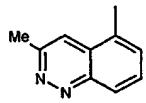
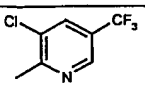
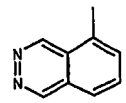
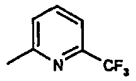
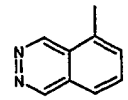
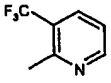
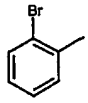
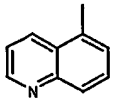
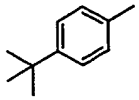
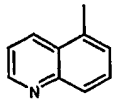
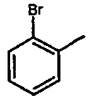
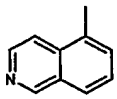
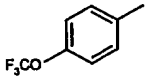
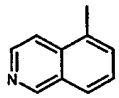
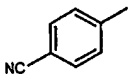
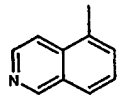
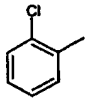
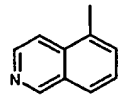
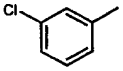
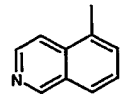
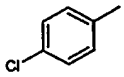
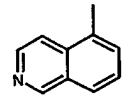
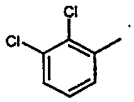
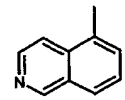
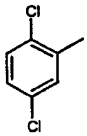
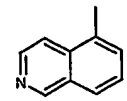
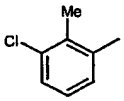
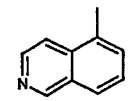
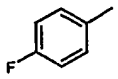
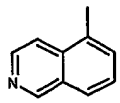
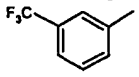
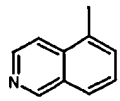
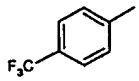
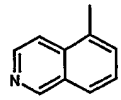
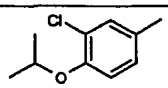
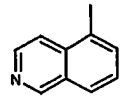
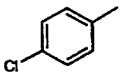
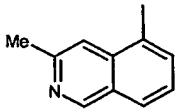
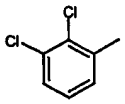
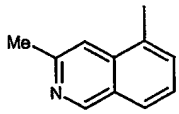
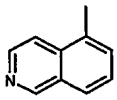
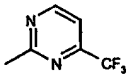
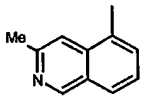
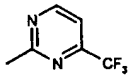
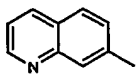
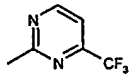
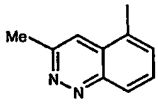
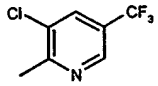
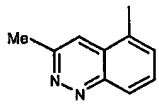
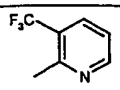
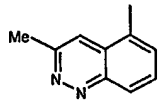
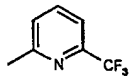
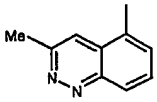
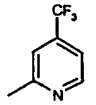
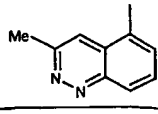
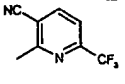
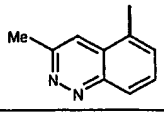
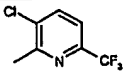
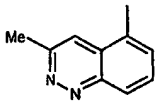
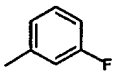
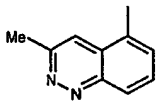
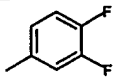
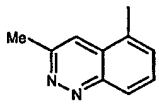
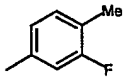
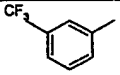
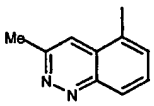
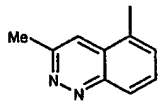
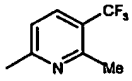
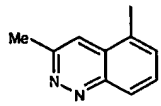
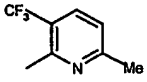
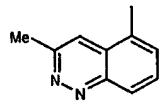
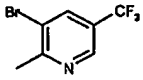
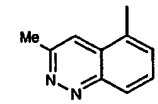
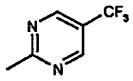
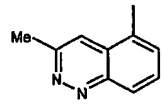
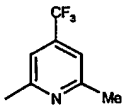
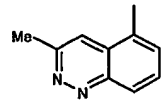
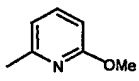
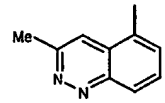
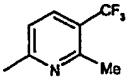
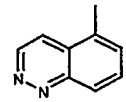
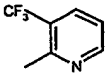
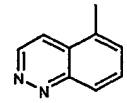
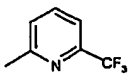
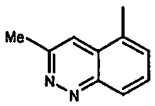
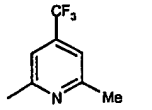
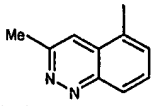
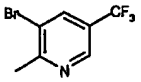
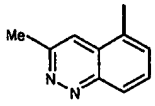
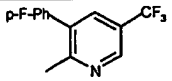
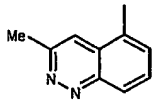
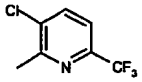
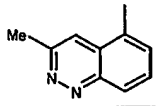
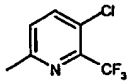
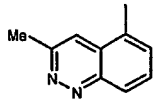
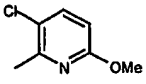
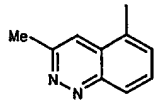
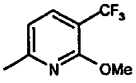
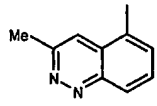
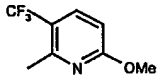
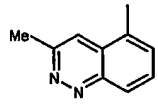
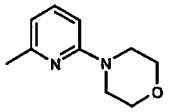
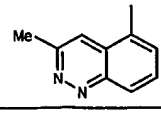
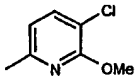
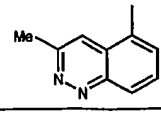
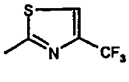
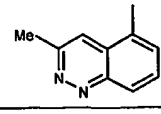
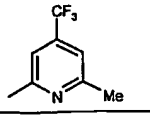
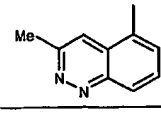
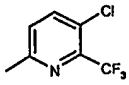
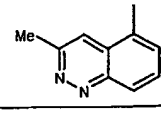
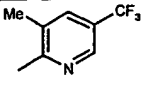
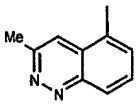
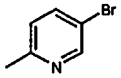
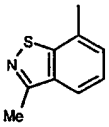
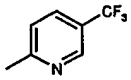
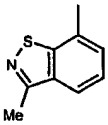
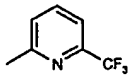
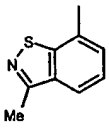
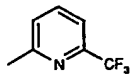
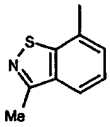
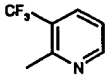
Ex		S'Chem	s	r		MH+
3		R	1	1		417
4		R	1	1		417
5		R	1	1		417
6		R	1	1		417
7		R	1	1		382, 384
8		R	1	1		382, 384
9		R	1	1		417
10		R	1	1		450, 452

11		R	1	1		403
12		R	1	1		403
13		R	1	1		411, 413
14		R	1	1		389
15		R	1	1		411, 413
16		R	1	1		417
17		R	1	1		358
18		R	1	1		366, 368
19		R	1	1		366, 368
20		R	1	1		366, 368
21		R	1	1		401, 403
22		R	1	1		401, 403
23		R	1	1		381, 383

24		R	1	1		351
25		R	1	1		401
26		R	1	1		401
27		R	1	1		424, 426
28		R	1	1		380, 382
29		R	1	1		415, 417
30		-	2	1		417
31		-	2	1		431
32		-	2	1		417
33		-	2	1		464, 466
34		-	2	1		431
35		-	2	1		431
36		-	2	1		431
37		-	2	1		456

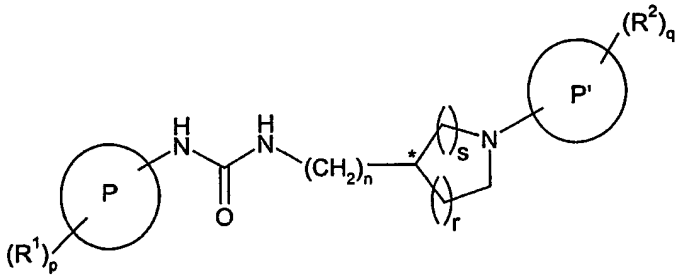
38		-	2	1		464, 468
39		R	1	1		366
40		R	1	1		384
41		R	1	1		380
42		R	1	1		416
43		R	1	1		431
44		R	1	1		431
45		R	1	1		495, 497
46		R	1	1		418
47		R	1	1		431
48		-	2	1		393
49		-	2	1		431
50		-	2	1		417
51		-	2	1		417

52		-	2	1		445
53		-	2	1		509, 511
54		-	2	1		525
55		-	2	1		465, 467
56		-	2	1		465, 467
57		-	2	1		427, 429
58		-	2	1		461
59		-	2	1		461
60		-	2	1		448
61		-	2	1		427, 429
62		-	2	1		437
63		R	1	1		431
64		R	1	1		450, 452
65		R	1	1		431

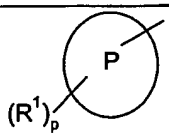
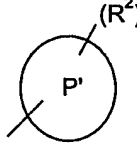
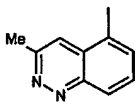
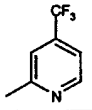
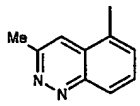
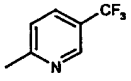
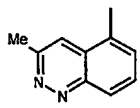
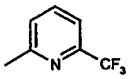
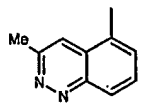
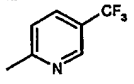
66		R	1	1		427, 429
67		R	1	1		422
68		R	1	1		422
69		-	2	1		436
70		-	2	1		436

The following Examples detailed in Table 2 (n = 1) below were prepared using similar methods to those described above.

Table 2



(I)

Ex		S'Chem	n	s	r		MH+
71		R	1	0	2		431
72		R	1	0	2		431
73		R	1	0	2		431
74		S	1	0	2		431

S'Chem = stereochemistry

Pharmacological Data

(a) In vitro assay

As referenced above, the compounds of the invention are vanilloid receptor (VR1) antagonists and hence have useful pharmaceutical properties. Vanilloid receptor (VR1) antagonist activity can be confirmed and demonstrated for any particular compound by use of conventional methods, for example those disclosed in standard reference texts such as D. Le Bars, M. Gozarin and S. W. Cadden, Pharmacological Reviews, 2001, 53(4), 597-652] or such other texts mentioned herein.

The screen used for the compounds of this invention was based upon a FLIPR based calcium assay, similar to that described by Smart et al. (British Journal of Pharmacology, 2000, 129, 227-230). Transfected astrocytoma 1321N1 cells, stably expressing human VR1, were seeded into FLIPR plates at 25,000cells/well (96-well plate) and cultured overnight.

The cells were subsequently loaded in medium containing 4μM Fluo-3 AM (Molecular Probes) for 2 hours, at room temperature, in the dark. The plates were then washed 4 times with Tyrode containing 1.5mM calcium, without probenecid.The cells were pre-incubated with compound or buffer control at room temperature for 30 minutes. Capsaicin (Sigma) was then added to the cells. Compounds having antagonist activity against the human VR1 were identified by detecting differences in fluorescence when measured after capsaicin addition, compared with no compound buffer controls. Thus, for example, in the buffer control capsaicin addition results in an increase in intracellular calcium concentration resulting in fluorescence. A compound having antagonist activity blocks the capsaicin binding to the receptor, there is no signalling and therefore no increase in intracellular calcium levels and consequently lower fluorescence. pKb values are generated from the IC_{50} values using the Cheng-Prusoff equation.

All compounds tested by the above methodology had pKb > 6, preferred compounds having a pKb > 7.0.

(b) FCA-induced hyperalgesia in the Guinea pig

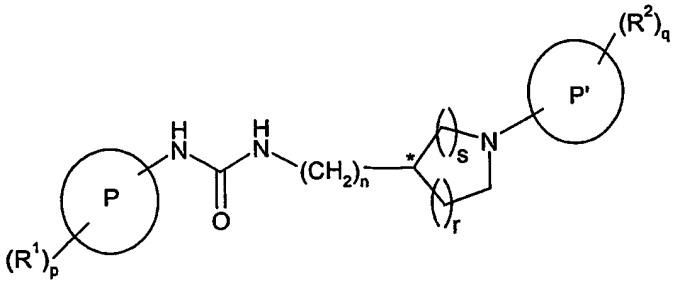
100µl of 1mg/ml FCA was injected intraplantar into the left paw of 4 groups of 8 male Dunkin Hartley guinea-pigs (batch: 6282434, average weight 340g). 24 hours later compounds were administered orally at 0 (vehicle), 3, 10 30mg/kg with vehicle as 1%methylcellulose and dosing volume being 2ml/kg and dosing straight into the stomach. The methylcellulose was added gradually to the compound into the pestle and mortar and ground together.

Behavioural readouts of mechanical hyperalgesia were obtained before FCA administration (naïve reading), after FCA but before drug administration (predose reading) and 1 hour after drug administration. The readout used was paw pressure (Randall-Sellito) and the end point was paw withdrawal. The paw pressure equipment also had one silver disc placed on the point to increase the markings by a factor of 2.

Compounds having a pKb > 7.0 *in vitro*, according to model (a) above, were tested in this model and shown to be active.

Claims

1. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:

P is selected from benzisothiazolyl, cinnolinyl, phenyl, phthalazinyl, quinazolinyl, quinolinyl or iso-quinolinyl;

P' is selected from cinnolinyl, phenyl, pyridazinyl, pyridinyl, pyrimidinyl, thiazolyl, quinolinyl or iso-quinolinyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, $-NO_2$, -OH, $-OCF_3$, $-CF_3$, $-NR^4R^5$, $-S(O)_mR^6$, $-S(O)_2NR^4R^5$, $-OS(O)_2R^6$, $-OS(O)_2CF_3$, $-O(CH_2)_xNR^4R^5$, $-C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, $-C(O)(CH_2)_xOR^6$, $-C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, $-C(O)NR^4R^5$, $-(CH_2)_xC(O)$alkoxy, $-(CH_2)_xOC(O)R^6$, $-(CH_2)_xOR^6$, $-(CH_2)_xR^4R^5$, $-(CH_2)_xC(O)NR^4R^5$, $-(CH_2)_xN(R^4)C(O)R^6$, $-(CH_2)_xS(O)_2NR^4R^5$, $-(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, $-(CH_2)_xS(O)_2R^6$, $-(OCH_2)_xS(O)_2R^6$, $-N(R^4)S(O)_2R^6$, $-N(R^4)C(O)R^6$, $-(CH_2)_xN(R^4)S(O)_2R^6$, $-(CH_2)_xN(R^4)C(O)R^6$ or $-(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

Z is a bond, O, S or NR^7;

R^6 is alkyl or aryl;

R^7 is hydrogen, alkyl or aryl;

Ar is phenyl, which may be optionally substituted by one or more halo atoms;

m is 1 or 2;

n is 0, 1, 2 or 3;

p and q are independently 0, 1, 2, 3 or 4;

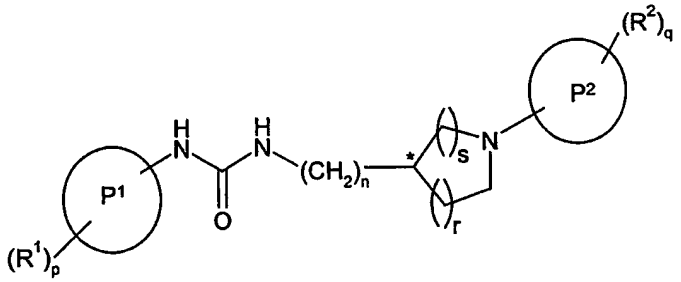
r is 1, 2 or 3;

s is 0, 1 or 2; and

x is 0, 1, 2, 3, 4, 5 or 6;

with the proviso that when P is phenyl, quinolinyl or iso-quinolinyl then P' is cinnolinyl, pyridazinyl, pyrimidinyl, thiazolyl, quinolinyl or iso-quinolinyl.

2. A compound of formula (I), as claimed in claim 1, of formula (IA),



(IA)

or a pharmaceutically acceptable salt thereof, or a solvate thereof, wherein:

P^1 is selected from benzisothiazolyl, cinnolinyl, phthalazinyl or quinazolinyl;

P^2 is selected from cinnolinyl, pyridazinyl, pyrimidinyl, thiazolyl, quinolinyl or iso-quinolinyl;

R^1 and R^2 are independently selected from –H, halo, alkyl, alkoxy, cycloalkyl, aralkyl, aralkoxy, cycloalkylalkyl, cycloalkylalkoxy, -CN, -NO_2, -OH, -OCF_3, -CF_3, -NR^4R^5, -$S(O)_mR^6$, -$S(O)_2NR^4R^5$, -$OS(O)_2R^6$, -$OS(O)_2CF_3$, -$O(CH_2)_xNR^4R^5$, -$C(O)CF_3$, -C(O)alkyl, -C(O)cycloalkyl, -C(O)aralkyl, -C(O)Ar, -$C(O)(CH_2)_xOR^6$, -$C(O)(CH_2)_xNR^4R^5$, -C(O)alkoxy, -$C(O)NR^4R^5$, -$(CH_2)_xC(O)$alkoxy, -$(CH_2)_xOC(O)R^6$, -$(CH_2)_xOR^6$, -$(CH_2)_xR^4R^5$, -$(CH_2)_xC(O)NR^4R^5$, -$(CH_2)_xN(R^4)C(O)R^6$, -$(CH_2)_xS(O)_2NR^4R^5$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -ZAr, -$(CH_2)_xS(O)_2R^6$, -$(OCH_2)_xS(O)_2R^6$, -$N(R^4)S(O)_2R^6$, -$N(R^4)C(O)R^6$, -$(CH_2)_xN(R^4)S(O)_2R^6$, -$(CH_2)_xN(R^4)C(O)R^6$ or –$(CH_2)_xC(O)$alkyl;

R^4 and R^5 may be the same or different and represent H or alkyl; or R^4 and R^5 together with the nitrogen atom to which they are attached form a heterocyclic ring;

Z is a bond, O, S or NR^7;

R^6 is alkyl or aryl;

R^7 is hydrogen, alkyl or aryl;

Ar is phenyl, which may be optionally substituted by one or more halo atoms;

m is 1 or 2;

n is 0, 1, 2 or 3;

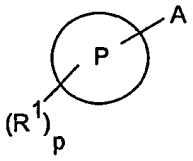
p and q are independently 0, 1, 2, 3 or 4;

r is 1, 2 or 3;

s is 0, 1 or 2; and

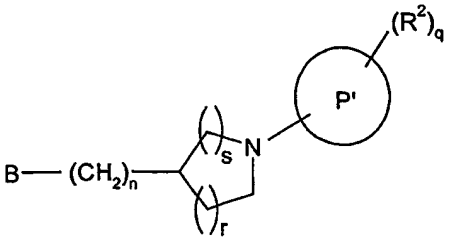
x is 0, 1, 2, 3, 4, 5 or 6.

3. A process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, which process comprises coupling a compound of formula (II):



(II)

in which R^1, P and p are as defined in formula (I) with a compound of formula (III):



(III)

in which P', R^2, n, q, r and s are as defined in formula (I) and A and B contain appropriate functional groups which are capable of reacting together to form the urea moiety;

and thereafter, as necessary, carrying out one or more of the following reactions:

(i) converting one compound of formula (I) into another compound of formula (I);

(ii) removing any protecting group;

(iii) preparing a salt or a solvate of the compound so formed.

4. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use as an active therapeutic substance.

5. A compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, for use in the treatment or prophylaxis of pain.

6. A method for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial, in mammals including humans, which comprises administering to a mammal in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1.

7. A method according to claim 6, for the treatment or prophylaxis of the Primary and Secondary Disorders of the invention.

8. Use of a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, in the manufacture of a medicament for the treatment or prophylaxis of disorders in which antagonism of the Vanilloid (VR1) receptor is beneficial.

9. Use according to claim 8, in the manufacture of a medicament for the treatment or prophylaxis of the Primary and Secondary Disorders of the invention.

10. A pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt or solvate thereof, as claimed in claim 1, and a pharmaceutically acceptable carrier or excipient therefor.

INTERNATIONAL SEARCH REPORT

Internat[illegible] Application No
PCT/EP 03/10262

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/04 C07D403/04 C07D403/12 C07D401/14 C07D403/14
C07D417/14 A61K31/4025 A61K31/428 A61K31/47 A61K31/517
A61K31/519 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 3 424 761 A (LUNSFORD CARL D ET AL) 28 January 1969 (1969-01-28) cited in the application the whole document ---	1-10
Y	MASTERS J J ET AL: "Non-Amidine-Containing 1,2-Dibenzamidobenzene Inhibitors of Human Factor Xa with Potent Anticoagulant and Antithrombotic Activity" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 43, 2000, pages 2087-2092, XP002238143 ISSN: 0022-2623 the whole document --- -/--	1-10

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 December 2003	14/01/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Gregoire, A

INTERNATIONAL SEARCH REPORT

Internati[illegible] Application No
PCT/EP 03/10262

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4 001 422 A (DANILEWICZ JOHN C ET AL) 4 January 1977 (1977-01-04) Claims and closest compound n°19 col 17	1-10
Y	WO 02 22592 A (SCHERING CORP) 21 March 2002 (2002-03-21) claims 1,2,10	1-10
P,X	WO 03 022809 A (RAMI HARSHAD KANTILAL ;WYMAN PAUL ADRIAN (GB); THOMPSON MERVYN (GB) 20 March 2003 (2003-03-20) cited in the application compound 77 page 45 the whole document	1-10
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E	WO 03 076421 A (MEERPOEL LIEVEN ;DE WINTER HANS LOUIS JOS (BE); JANSSEN PHARMACEUT) 18 September 2003 (2003-09-18) intermediate 9 page 31	1,2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/10262

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 6 and 7 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internat[illegible] Application No
PCT/EP 03/10262

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